Swami Ramanand Teerth Marathwada University, Nanded.

(UGC recognised, NAAC Re-accredited 'B++' grade state university)

"SYNTHESIS AND PHARMACOLOGICAL STUDY OF NOVEL HETEROCYCLES CONTAINING SULPHUR, NITROGEN AND OXYGEN ATOMS"

Research Proposal submitted
In partial fulfilment of registration to

Ph.D. Programme
In the subject
CHEMISTRY faculty of Science and Technology

Submitted by

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Research Proposal

Title of the proposed Research work:

"Synthesis and pharmacological study of Novel heterocycles containing Sulphur, Nitrogen and Oxygen atoms"

Abstract of the proposed Research work:

In the proposed work new Schiff bases will be synthesized by condensation of aromatic aldehydes and aromatic primary amines for the Schiff bases will be converted into 4-Thiazolidinones, and 1,3-benzoxazines. Polyhydroquinoline Derivatives will be synthesized from Dimedone. Structure of the compounds will be confirmed by elemental analysis and spectral studies. Synthesized compounds will be screened for their pharmacological activity.

1. Introduction:

Heterocyclic compounds are a structural component of a vast number of biologically active natural and unnatural compounds, medicinally important compounds and organic materials[1]. In fact, more than half of all known organic compounds are heterocycles. The heterocyclic compounds having five or six membered ring containing nitrogen, sulphur and oxygen as a hetero atom shows remarkable activities such as antifungal, anti-cancer, antipyretic, anti- HIV, anti-tuberculosis, anti-inflammatory, antioxidant anti-androgenic and analgesic.

4- Thiazolidinone containing β-lactum ring with Sulphur atom and derivatives inhibits the biosynthesis of peptidoglycan polymer essential for cell wall of bacteria on inactivation of MurB enzyme. MurB enzyme is a unique target for antibacterial activity of 4-Thiazolidinone. Various synthetic approaches of 4-Thiazolidinones were reported.

1,3-benzoxazines are useful and important heterocycles utilised in drug research due to their variety of biological activities such as anti- inflammatory, analgesic, homicidal, anti-fertility, hypnotic and sedative. Schiff 's bases have been used successfully in the synthesis of sulphur,

nitrogen and oxygen containing heterocycles such as 4-Thiazolidinones and 1,3-benzoxazines.

Polyhydroquinoline Derivatives Polyhydroquinolines are structurally related to 1,4-dihydropyridine (DHP) which is a pyridine molecule. The polyhydroquinoline nucleus is paying considerable attention recently due to its encouraging activities such as antihypertensive activity, cardiovascular agents, bronchodilators, geroprotective, hepatoprotective agents, neuroprotectants, antiplatelet aggregators, cerebral anti-ischemic agents and chemo sensitizers, alzheimer's disease[2], anticancer[3] and antimicrobial agent[4], vasodilators, anti-atherosclerotic and antidiabetic agent[5], anti-inflammatory [6], antifungal[7] activities.

On the origin of these ideas we have the stimulus to synthesize some novel Schiff Bases,4-Thiazolidinones, 1,3-benzoxazines and Polyhydroquinoline derivatives expecting better pharmacological activities. Structure of the newly synthesized compounds will be confirmed by elemental analysis and spectral studies. Synthesized compounds will be screened for their pharmacological activity.

2. Review of literature and development in the relevent subject:

Literature survey reveals that various Schiff's bases, 4-Thiazolidinone, 1,3-benzoxazines and Polyhydroquinoline derivatives have been found to be possess different pharmacological activities. A brief review of literature is given as follows.

Junne S.B.*et al*[8]. reported the novel heterocyclic Schiff's bases, 4-Thiazolidinones exhibited antibacterial and antifungal activities. Archana B. Kadam *et al*[9] derived a series of new Schiff bases and screened their antimicrobial activity. Junne S. B.*et al*[10]synthesized halo substituted Schiff bases and screened their antibacterial activity. A.P. Rajput and P.D. Girase[11] derived a series of new 4-Thiazolidinones from bis-Schiff bases and screened their antimicrobial activity. N. Siva Subramanian *et al*[12] have synthesized novel thaizolidino S-fused compounds and screened their antibacterial and antifungal activity.

Tej Prakash Singh *et al*[13]. prepared 4-thiazolidinone derivatives and evaluated for their different types of pharmacological activities like cytotoxic activity, antimicrobial activity anticancer activity, anticonvulsant activity, anti- inflammatory activity, analgesic activity. Karel Waisser et al[14]. have synthesized 6-chloro-3-phenyl-4-thioxo-2H-1,3-benzoxazine-2(3H)-ones and 6-chloro-3-phenyl-2H-1,3-benzoxazine-2,4(3H)-dithiones.

Y.B. Vibhute et al[15] have synthesized 1,3-benzoxazinesfrom Schiff bases. Faramarz Rostami-Charati[16]synthesized of 1,3-benzoxazine derivatives via three-component reaction of isocyanide and isoquinoline with 1-(6-hydroxy-2-isopropenyl-1-benzofuran-yl)-1-ethanone or 4-hydroxycumarine in water in the presence of piperidine at 70°C is reported. Satoshi yamamoto*et al* [17], Synthesized a new series of 1, 3-benzoxazine derivatives with a 2-pyridine 1-oxide group at C4 was designed to explore novel K^+ channel openers. Sabakhi I.,*et al.*[18] reported design, synthesis and biological evaluation of new 1, 4-Dihydropyridine (DHP) derivatives as selective cyclooxygenase-2 inhibitors. Harvinder Singh Sohal*et al.*[19] carried out multi-component approach for the synthesis of fused dihydropyridines through unsymmetrical Hantzsch condensation consuming glycerol as green solvent. Suman L. Jain *et al.*[20] reported combined thiourea dioxide water an effective recyclable catalyst for the catalysis of polyhydroquinolines through Hantzsch multicomponent coupling thiourea dioxide in water was found to be an effectual and recyclable organocatalytic system for the one-pot synthesis of polyhydroquinoline derivatives through the Hantzsch-type coupling of aldehyde, dimedone, acetoacetate and ammonium acetate underneath slight reaction circumstances. G.Safaei-Ghomi and M. A. Ghasemzadeh[21] reported efficient and ecologically approachable technique for the one-pot synthesis of polyhydroquinolines has been established in the existence of CuO nanoparticles. B. P. Bandgar *et al.*[22] reported highly efficient synthesis of polyhydroquinoline derivatives carried out through four component reaction of aldehydes, dimedone, ethyl acetoacetate , and ammonium acetate in refluxing water. Excellent yields of the products and easier work-up are attractive features of this green procedure.

3. Importance of study:

To synthesize new Schiff bases,4-Thiazolidinone, 1,3-benzoxazines and Polyhydroquinoline derivatives expecting promising pharmacological activities. Proposed compounds expected to be antifungal, anticancer, antiviral, anti-HIV, antituberculsis, anti-inflammatory, antioxidant, antiandrogenicgero protective, hepatoprotective agents, neuroprotectants and analgesic activities.

Now a days there is burring problem to control the deadly diseases like AIDS, cancer and tuberculosis.4-Thiazolidinone and other heterocycles are known to inhibit cell cycle mainly inactivating ribonucleotide reductase, an enzyme that mediates the conversion of ribonucleotides to deoxyribonucleotides. It inhibits the uncontrolled growth of cells. Hence,

these compounds might be act as anticancer drug. 1,3-benzoxazines exhibit in vitro activity against Mycobacerium tuberculosis. building block in pharmaceutical chemistry.

At present control of AIDS, cancer and tuberculosis is burring problem to the society. Hence, this work has National and international status.

4. Objectives of the proposed research work:

Our objectives of the proposed work are:

Hypothesis and Research Methodology:

- To prepare Schiff bases from substituted aromatic amines and aromatic aldehydes in optimized reaction condition.
- To synthesize 4-thiazolidinones from Schiff bases by using Mercaptoacetic acid and $ZnCl_2$ as a catalyst.
- To synthesis of 1,3 Benzoxazine from Schiff base under optimized condition and characterized by spectral analysis.
- To prepare Polyhydroquanazoline derivatives.
- To analyze theof newly synthesized heterocyclic compounds by elemental and spectral analysis by using proper instruments.
- To study the different pharmacological activities of newly synthesized heterocyclic compounds.
- In the proposed work new Schiff bases will be synthesized by condensation of aromatic aldehydes and aromatic primary amines for the Schiff bases will be converted into 4-Thiazolidinones, and 1,3-benzoxazines. Polyhydroquinoline derivatives will be synthesized from dimedone. All heterocyclic compounds will be synthesized by conventional method.

Limitations:

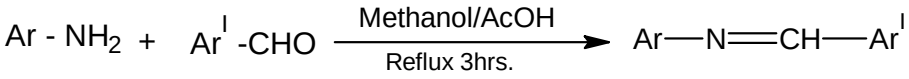
- The thorough reading of literature reveals that synthesis of Some heterocyclic compounds requires harsh reaction conditions, such as high temperatures or strong acids/bases. These conditions might not be compatible with sensitive functional groups or biomolecules, limiting the scope of the reaction.
- Also challenges may be faced while developing high-yielding and efficient synthetic routes to heterocyclic compounds. Reaction yields might be limited due to side reactions, equilibrium limitations, or difficulties in isolating and purifying products.

Expected outcome:

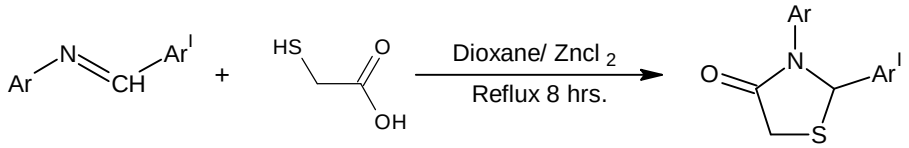
- In current scenario scientist are trying to synthesize novel heterocyclic compounds which are beneficial to society. Therefore, the successful completion of the proposed research work would result in to promising pharmacological activities such as antifungal, anticancer, antiviral, antipyretic, anti-inflammatory, antioxidant and analgesic activities.

5. Proposed work plan with Scheme:

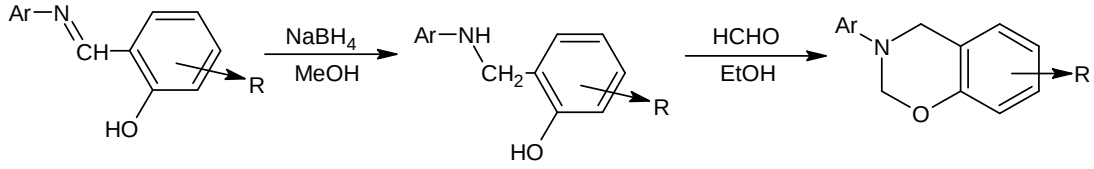
Scheme-I: Schiff Bases



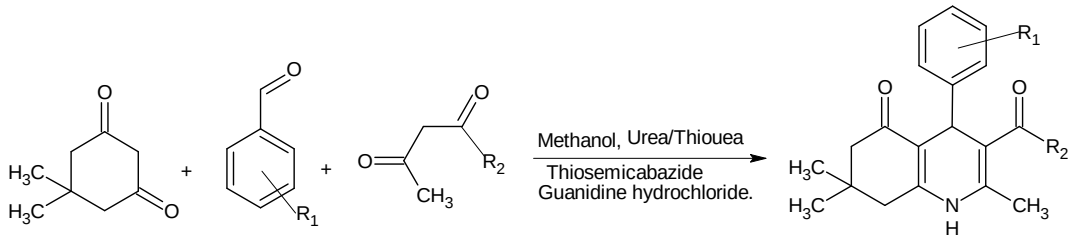
Scheme-II: 4-Thiazolidinones



Scheme-III: 1,3-Benzoxazine



Scheme-IV: Polyhydroquinoline Derivatives



6. Proposed work plan / formulation and structure of study:

First Year: Reference work, synthesis of Schiff bases, 4-Thiazolidinones, spectral and analytical studies of newly synthesized Schiff bases and 4-Thiazolidinones.

Second Year: Synthesis of 1,3-benzoxazines, Polyhydroquinoline Derivatives andtheir spectral analytical studies of newly synthesized compounds.

Third year: Study the various pharmacological activities of newly synthesized heterocyclic compounds.

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Research Scholar **Research Guide**

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